Evaluation of Acute Mountain Sickness by Unsedated Transnasal Esophagogastroduodenoscopy at High Altitude

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Abstract: BACKGROUND AIMS It is not clear how rapid ascent to high altitude causes the gastrointestinal symptoms of acute mountain sickness (AMS). We assessed the incidence of endoscopic lesions in the upper gastrointestinal tract in healthy mountaineers after rapid ascent to high altitude, their association with symptoms, and their pathogenic mechanisms. METHODS In a prospective study, 25 mountaineers (10 female; mean age, 43.8y±9.5 y) underwent unsedated, transnasal esophago-gastroduodenoscopy in Zurich (490 m) and then on 2 test days (days 2 and 4) at a high altitude laboratory in the Alps (Capanna Regina Margherita, 4559 m). Symptoms were assessed using validated instruments for AMS (the AMS-C and the Lake Louise scoring system) and visual analogue scales (0-100). Levels of mRNAs in duodenal biopsies were measured by qPCR. RESULTS The follow-up endoscopy at high altitude was performed in 19/25 patients on day 2 and in 23/25 patients on day 4. Frequency of endoscopic lesions increased from 12% at baseline to 26.3% on day 2 and 60.9% on day 4 (P<0.001). The incidence of ulcer disease increased from 0 at baseline to 10.5% on day 2 and 21.7% on day 4 (P=.014). Mucosal lesions were associated with lower hunger scores (37.3 vs. 67.4 in patients without lesions; P=.012). Subjects with peptic lesions had higher levels of HIF2A mRNA, which encodes a hypoxia-induced transcription factor, and ICAM1 mRNA, which encodes an adhesion molecule, compared with subjects without lesions (fold changes: 1.38 vs 0.63; P=.001 and 1.37 vs 0.66; P=.011). CONCLUSIONS In a prospective study of 25 mountaineers, fast ascent to high altitude resulted in rapid onset of clinically meaningful mucosal lesions and ulcer disease. Duodenal biopsies from these subjects had increased levels of HIF2A mRNA and ICAM1 mRNA, which might contribute to formation of hypoxia-induced peptic lesions. Further studies are needed of the mechanisms of this process.

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ABBREVIATIONS:

AMS: acute mountain sickness

AMS-C: acute mountain sickness score

BMI: body mass index

CRP: C-reactive protein

EGD: esophagogastroduodenoscopy

GI: gastrointestinal

HAPE: high altitude pulmonary edema

IBD: inflammatory bowel disease

IQR: interquartile range

LLSAS: Lake Louise acute mountain sickness score

mRNA: messenger RNA

NSAIDs: non-steroidal anti-inflammatory drugs

O_2 Hb: oxyhemoglobin

pCO2: partial pressure of carbon dioxide

pO2: partial pressure of oxygen

PPI: proton pump inhibitor

qPCR: quantitative polymerase-chain-reaction

RNA: ribonucleic acid

SD: standard deviation

SpO2: oxygen saturation

VAS: visual analogue scale

ABSTRACT

Background & Aims: It is not clear how rapid ascent to high altitude causes the gastrointestinal symptoms of acute mountain sickness (AMS). We assessed the incidence of endoscopic lesions in the upper gastrointestinal tract in healthy mountaineers after rapid ascent to high altitude, their association with symptoms, and their pathogenic mechanisms.

Methods: In a prospective study, 25 mountaineers (10 female; mean age, 43.8y±9.5 y) underwent unsedated, transnasal esophago-gastroduodenoscopy in Zurich (490 m) and then on 2 test days (days 2 and 4) at a high altitude laboratory in the Alps (Capanna Regina Margherita, 4559 m). Symptoms were assessed using validated instruments for AMS (the AMS-C and the Lake Louise scoring system) and visual analogue scales (0–100). Levels of mRNAs in duodenal biopsies were measured by qPCR.

Results: The follow-up endoscopy at high altitude was performed in 19/25 patients on day 2 and in 23/25 patients on day 4. Frequency of endoscopic lesions increased from 12% at baseline to 26.3% on day 2 and 60.9% on day 4 (*P<0.001*). The incidence of ulcer disease increased from 0 at baseline to 10.5% on day 2 and 21.7% on day 4 (*P*=.014). Mucosal lesions were associated with lower hunger scores (37.3 vs. 67.4 in patients without lesions; *P*=.012). Subjects with peptic lesions had higher levels of *HIF2A* mRNA, which encodes a hypoxia-induced transcription factor, and *ICAM1* mRNA, which encodes an adhesion molecule, compared with subjects without lesions (fold changes: 1.38 vs 0.63; *P*=.001 and 1.37 vs 0.66; *P*=.011).

Conclusions: In a prospective study of 25 mountaineers, fast ascent to high altitude resulted in rapid onset of clinically meaningful mucosal lesions and ulcer disease. Duodenal biopsies from these subjects had increased levels of *HIF2A* mRNA and *ICAM1* mRNA, which might contribute to formation of hypoxia-induced peptic lesions. This axis warrants further mechanistic studies.

KEY WORDS: EGD, stomach, intercellular adhesion molecule, endothelial PAS domain protein 1

Need to Know

Background: It is not clear how rapid ascent to high altitude causes the gastrointestinal symptoms of acute mountain sickness.

Findings: In a prospective study of 25 mountaineers, we found that rapid ascent to high altitude (4559 m) resulted in mucosal lesions and ulcer disease. Duodenal biopsies from these subjects had increased levels of *HIF2A* mRNA and *ICAM1* mRNA, which might contribute to formation of hypoxia-induced peptic lesions.

Implications for patient care: Mountaineers should be careful to ascend too rapidly, to avoid peptic ulcer disease and damage to the intestinal mucosa. Similar mechanisms might contribute to inflammatory bowel disease flares in high altitude.

INTRODUCTION

Rapid ascent to high altitude levels is a particular risk factor for the development of acute mountain sickness (AMS).[1] Both, experienced mountaineers and tourists rapidly traveling to high altitude areas such as the Andes, Alps or the Himalaya are affected. Gastrointestinal manifestations are cardinal symptoms of AMS.[2,3] However, causes and pathophysiology of gastrointestinal symptoms of AMS remain elusive, but may include direct effects of hypobaric hypoxia on mucosal integrity.[4]

Acute mountain sickness is a disease that occurs within the very first days after arrival above 2500 meters.[2] Typical symptoms include headache, anorexia, nausea, vomiting, dizziness and malaise.[3] Prevalence of AMS is estimated at 10-25%, but increases to 50-85% at elevations above 4500-5500m.[5-7] Risk factors for the development of AMS are a past medical history of AMS, rapid ascent (≥625m per day), lack of acclimatization, female sex and young age.[8-10] Gastrointestinal symptoms occur in more than 80% of patients with AMS (particularly nausea and vomiting).[11] In addition, high rates of peptic ulcer disease have been described in native highlanders in the Peruvian Andes.[11] Furthermore, upper gastrointestinal bleeding from peptic ulcer disease appears to be a frequent problem in high altitude areas.[12] Hypoxia might be an important factor contributing to the development of peptic ulcerations, but its exact role remains unclear. In addition, it has yet to be determined whether GI symptoms of AMS are based on GI lesions or rather have a pure central nervous system origin.

While AMS usually occurs in healthy individuals, high altitude exposure has been recently demonstrated to be associated with flare-ups in patients with inflammatory bowel disease (IBD).[13,14] Both ascent to above 2000m and commercial flights, which correspond to an altitude of 1800-2300m, correlated with a flare of IBD symptoms. However, the link between hypoxia and intestinal inflammation appears to be complex. At the molecular level, the heterodimeric hypoxia-induced factors *HIF1*, and *HIF2* have opposite functions and work as a “switching modulator”, but the dynamic regulation of these factors remains unclear.[15] Chronic activation of *HIF2* increases pro-inflammatory cytokines and is associated with intestinal injury, while *HIF1* activation in colitis leads to a protective response.[16,17] Therefore, it is uncertain whether *HIF* activation by short-term hypoxia (such as after rapid ascent to high altitude) leads to mucosal inflammation, loss of mucosal integrity or whether this system protects against intestinal injury.

Given these uncertainties, we sought to answer the following questions: i) What is the incidence of peptic lesions in healthy mountaineers after rapid ascent to 4559m? ii) Are these peptic lesions associated with GI symptoms? iii) What mRNA changes of target genes can be seen with the development of peptic lesions?

METHODS

Study design

This was a prospective, non-randomized study with healthy mountaineers who underwent esophago-gastroduodenoscopy (EGD) at 490m and on two test days (d2 and d4) at Capanna Regina Margherita high altitude laboratory in the Alps (4559m, **Supplementary File 1**) upon rapid ascent from 1130m. This analysis represents the endoscopy arm of a larger clinical project. Other sub-studies emerging from the project (including studies on nutrition and high altitude sickness) have been reported elsewhere.[18-20] The study was approved by the local ethics committee of the University of Zurich (EK-1677). Written informed consent was obtained from all participants before inclusion into the study.

Study subjects

Details on subject recruitment and study enrolment have been published elsewhere.[18,19] Briefly, healthy mountaineers were recruited through alpine magazines and using a registry of Air Zermatt (a Swiss air rescue) that included people rescued for high altitude disease in the past 5 years. The following exclusion criteria were applied: 1) subjects spent more than 3 nights above 2500m within one month before study enrolment; 2) subjects had chronic diseases requiring ANY regular medication; 3) subjects adhered to dietary restrictions that could not be upheld in the high altitude laboratory (such as gluten-free, vegetarian or lactose-free diet); and 4) age below 18 or above 65 years. On demand intake of drugs such as paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) was not an exclusion criterion.

Data collection

For the purpose of this study, the following data were collected: 1) demographics being sex, age, body mass index (BMI); 2) history of high altitude pulmonary edema (HAPE);[21] 3) oxygen levels using pulse oximetry (Infinity, Dräger, Liebefeld, Switzerland) and arterial blood gas analysis (AVL 5 Radiometer, Copenhagen, Denmark); 4) symptoms of AMS using two validated instruments, the cerebral-sensitive score of the Environmental Symptom

Questionnaire (AMS-C) and the Lake Louise scoring system (LLSAS);[22] 5) gastrointestinal symptoms (hunger, dyspepsia) using 10cm visual analogue scales and being reported as values ranging from 0 (lowest) to 100 (highest); and 6) laboratory values (lactate, C-reactive protein (CRP)). Data were collected at baseline at 490m and days 2 and 4 after ascent to 4559m. After each endoscopy at 4559m, an ad libitum meal was given to the subjects and total calorie intake (kcal) was measured. Medications (dexamethasone, acetaminophen and NSAIDs) were started based on predefined criteria (**Supplementary Methods**).

Endoscopy

Subjects underwent transnasal fiberoptic EGD (FG-16V, 5.3mm, Pentax, Tokio, Japan) under lidocaine nasal analgesia and 2L oxygen supplement in Zurich (490m) and on two test days (d2 and d4) at Capanna Regina Margherita (4559m), where they spent four days after rapid ascent from 1130m. For details and endoscopic evaluation, see **Supplementary Methods**.

Molecular analyses

mRNA levels of 18 proinflammatory and hypoxia-related genes were measured from duodenal biopsies of normally appearing mucosa (**Supplementary Methods**).

Statistics

For all statistical analyses, IBM SPSS software (version 22.0.0, 2013 SPSS Science, Chicago, IL) was used. For the purpose of this study, a p-value of <0.05 was considered statistically significant. For details see **Supplementary Methods.**

RESULTS

Patient demographics and baseline characteristics

We included a total of 25 patients (mean age 43.8y±9.5, 10 females (40%), mean BMI 23.8kg/m^2±2.2). Eight patients had a previous history of HAPE (32%). One patient took NSAIDs at baseline. None of the patients reported intake of PPI. For baseline characteristics, see **Table 1**. Endoscopy was performed in all 25 patients. In one patient, mild reflux esophagitis was seen, while in two patients erythema in the stomach was detected. Otherwise, EGD was considered to be normal.

AMS score and medication at 4559m

AMS-C and LLSAS scores on day 2 (0.56 vs 0, $p<0.001$, 5 vs 1, $p<0.001$) and on day 4 (0.26 vs 0, $p=0.002$, and 3 vs 1, $p=0.003$) were significantly higher than at baseline in Zurich.

No significant differences regarding hunger (baseline 38.2, d2 48.8, d4 49.6) and dyspepsia scores (baseline 28.4, d2 39.0, d4 22.2) were detected. Lactate and CRP levels were significantly higher at both, day 2 (1.0 vs 0.9 p=0.016 and 2.9 vs 0.7 p<0.001) and day 4 (1.3 vs 0.9 p=0.009 and 2.8 vs 0.7 p<0.001) compared to baseline. Dexamethasone was applied to 14 patients. Two patients were on NSAIDs at day 2, and three at day 4, while seven patients were put on PPI. Nine patients were taking acetaminophen (Paracetamol) at day 2 and four at day 4.

Endoscopy at 4559m

19/25 patients underwent endoscopic examination at day 2 and 23/25 at day 4. Two patients did not have any follow-up endoscopy at all. The procedure was generally well tolerated and safe. No complications occurred despite significantly lower oxygenation: Arterial SpO_2 was lower at day 2 and day 4 (76.4 vs 97.3% p<0.001 and 81.1 vs 97.3% p<0.001) with lower pO_2 (39.0 vs 91.5mmHg p<0.001 and 44.3 vs 91.5mmHg p<0.001) and O_2Hb (76.4 vs 95.0% p<0.001 and 80.5 vs 95.0% p<0.001) compared to baseline (Zurich). The findings during d2, d4 follow-up endoscopy are summarized in **Figure 1**. At day 2, new mucosal lesions were seen in 5 patients (2 patients with new lesions in the stomach and 5 patients with new lesions in the duodenum). Duodenal ulcers developed in 2 patients (1 patient with three ulcers), no gastric ulcer was detected. At day 4, new mucosal lesions (compared to baseline) were seen in 12 patients (9 patients with new lesions in the stomach, and 7 patients with new lesions in the duodenum). Gastric ulcers were seen in 3 patients, and duodenal ulcers were detected in 3 patients (1 patient with 6 duodenal ulcerations). Compared to the first endoscopy at d2, new lesions were seen in 9 patients (gastric lesions in 7 patients, duodenal lesions in 4 patients). New ulcers developed in 4 patients. Gastric lesions were successfully treated with PPI in one patient, while duodenal ulcers showed complete remission in another patient. In a third patient receiving PPI between day 2 and 4, gastric erosion and duodenal ulcer did not show any response. Taken together, frequency of endoscopic lesions increased from 12% (baseline) to 26.3% (d2) and 60.9% (d4), while the incidence of peptic ulcer disease rose from 0.0% to 10.5% (d2) and 21.7% (d4). When looking at patients without intake of ulcerogenic medication (NSAIDs, dexamethasone) at the time of endoscopy, these rates were 8.3% (baseline), 17.6% (d2) and 50% (d4) for endoscopic lesions and 0.0% (baseline), 5.9% (d2) and 12.5% (d4) for ulcerations. **Figure 2** shows

representative pictures for the development of erosions and ulcerations in the duodenum at 4559m.

Factors associated with development of endoscopic lesions at day 4

Subjects with peptic lesions on day 4 had significantly lower hunger scores than those with normal EGD measured as VAS 0-100 (37.3 vs 67.4, p=0.012, **Table 2**). Nevertheless, both groups were still able to eat a full meal with no significant difference regarding total calorie intake (802.1 vs 902.5kcal, n.s.). In addition, lesions were not associated with nausea, bloating, pain, fullness, AMS-C/LLSAS scores, oxygenation levels or with the use of medications (NSAIDs, dexamethasone, paracetamol). Per our protocol, a significantly larger proportion of patients with endoscopic lesions were put on PPI (0 vs 50%, p=0.011). There were no differences when only ulcerations (vs. no endoscopic ulceration) were analysed. No predictive factor for the development of mucosal lesions was identified using univariate and multivariate logistic regression modelling. Results for factors associated with development of endoscopic lesions at day 2 are shown in **Supplementary Table 1.**

mRNA analyses

To assess changes in duodenal mRNA levels with regards to development of peptic lesions, we excluded all subjects with endoscopically detected lesions at baseline and tested mRNA levels for 18 different target genes (**Figure 3**). mRNA analyses were available for 15 patients. Of those, 4 patients had a peptic lesion at day 2 and 9 at day 4. Subjects that developed peptic lesions at day 2, had higher *HIF2A* and *ICAM1* mRNA levels (**Figure 3**). While subjects without peptic lesions showed a decrease of their *HIF2A* and *ICAM1* mRNA levels compared to baseline (fold change 0.63 and 0.66), those with lesions had an increase in mRNA levels for both genes (fold change 1.38 and 1.37, p=0.0012 and p=0.011, **Figure 4**). *HIF2A* increase remained statistically significant after correction for multiple testing (p value for significance after Bonferroni correction = 0.0014). There were no differences with regards to other factors and cytokines (*HIF1A*, *FOXP3, IL6, IFNγ, NOD2* or *TNF)*.

DISCUSSSION

The exact causes of gastrointestinal symptoms of AMS are unknown, but may include direct effects of hypoxia on mucosal integrity. To assess incidence of peptic lesions, their association with GI symptoms, and possible pathogenic mechanisms, we clinically, endoscopically and molecularly analyzed healthy mountaineers after rapid ascent to 4559m.

The main findings of this study are: i) development of peptic lesions including peptic ulcer disease is frequently observed within two to four days after fast ascent to high altitude; ii) presence of mucosal lesions is associated with lower hunger scores, but no other AMS symptoms; and iii) patients with peptic lesions show higher *HIF2A* and *ICAM1* mRNA levels compared to patients with normal endoscopy.

We herein demonstrate, that development of peptic lesions is frequently observed within only two to four days after rapid ascent to high altitude. Being clinically relevant, these lesions can contribute to gastrointestinal symptoms at high altitude. Indeed, incidence of mucosal lesions increased from 12% at baseline to 26.3% at day 2 and 60.9% at day 4 after ascent to 4559m. Despite PPI treatment, incidence of endoscopic lesions steadily increased over time, which emphasizes on the relative contribution of hypoxia rather than acid secretion. In addition, peptic ulcer disease (baseline 0%) was observed in 10.5% at day 2 and 21.7% at day 4. Thus, one out of five patients developed peptic ulcer disease over this short period of time. These findings imply a negative impact of hypobaric hypoxia on mucosal integrity resulting from fast ascent to high altitude. This is particularly noteworthy given the current approach of treating AMS symptoms with ulcerogenic medication (NSAIDs, dexamethasone) that negatively affect mucosal integrity.[23,24] Based on our data, these drugs should be used with caution. Further, these findings give a rationale for flare-ups in IBD patients after flights and ascents to high altitude.[13,14] While for various reasons it is not feasible to perform colonoscopy in a high altitude laboratory, it is likely that similar lesions would be detected in response to hypobaric hypoxia triggering increased IBD symptoms.

Patients with peptic lesions showed higher *HIF2A* and *ICAM1* mRNA levels compared to subjects with normal endoscopy. In contrast, HIF1α mRNA levels were neither in- nor decreased. *HIF1A* and *HIF2A* are important regulators in response to hypoxia. They appear to have non-redundant functions by modulating transcription of an overlapping, but distinct set of genes.[25] In a simplified model, activation of *HIF1* leads to a protective response with beneficial effects on epithelial barrier function, while *HIF2* triggers pro-inflammatory cytokines and epithelial injury.[16,17,26-30] Depending on which factor is preferentially activated, hypoxia has beneficial or detrimental effects. *HIF2A* has been shown to correlate with increased pro-inflammatory cytokine expression in gastroesophageal reflux disease, while *HIF1A* is repressed in active eosinophilic esophagitis.[28,30] Of note, differences in mRNA levels between *HIF1A* and *HIF2A* were detected after rapid ascent to high altitude in our study.

HIF2A with its known detrimental effects on mucosal integrity appears to be a contributing factor to the development of mucosal lesions in the upper GI tract. Interestingly, the *HIF2* target *ICAM1* also showed such upregulation in subjects with endoscopically detected lesions. *ICAM1* is a transmembranous glycoprotein that binds to integrins expressed on inflammatory cells and thereby contributes to leukocyte adhesion, migration and stimulation.[31,32] As adhesion molecule, it has an important role in lymphocyte trafficking in the GI tract.[33] *ICAM1* has been previously shown to be induced by hypoxia. This hypoxic upregulation of *ICAM1* can be blocked by siRNA against *HIF2A*.[34] Previous studies have shown up-regulation of several pro-inflammatory cytokines in the context of hypoxia, beyond *ICAM1* expression. However, the interplay between hypoxia and inflammation is complex; and several factors may have affected our results. 1) Inflammatory factor production in response to hypoxia appears to be time-dependent;[35] and 2) short-term and chronic hypoxia have been shown to have opposite effects with regards to inflammation (pro-vs. anti-inflammatory). The cut-off values used in a previous study to define short-term hypoxia was 24 hours, while chronic hypoxia was defined by hypoxia duration of 10 days.[36] Our 2 and 4 days are somewhere in between, which might explain upregulation of some, but not all pro-inflammatory cytokines. This could also explain, why we did not detect decreases in *HIF1A* mRNA levels as it has been previously shown in the upper gastrointestinal tract in response to hypoxia.[28] In addition, findings from in vitro and pressure chamber experiments cannot be extrapolated 1:1 to high altitude exposure. Previous high altitude studies have further focused on blood samples rather than gastric tissue in particular.[37] Based on our findings, we speculate that the *HIF2-ICAM1* axis contributes to the development of peptic ulcer disease per se and to development of flares in IBD patients after flights and ascents to high altitude. Drugs selectively targeting *HIF2A* may be promising agents for these conditions.

Our study has strengths and limitations. To the best of our knowledge, this is the first time that upper endoscopy was performed after fast ascent to a high altitude laboratory. We herein show that unsedated transnasal EGD at 4559m is feasible and safe. Repetitive endoscopies made it possible to assess the dynamic development of peptic lesions and ulcers over time. This is particularly important given the presence of endoscopic abnormalities in healthy controls, which might be as high as 18%.[38] One major limitation is the fact that only duodenal samples were collected and that the biopsies were not taken

from the endoscopic lesion due to safety concerns at 4559m. However, since subjects were all healthy volunteers, we assume that hypoxia was evenly distributed throughout the stomach and duodenum. Due to logistic restrictions at 4559m, biopsies were immediately snap frozen in liquid nitrogen and therefore not accessible for histological evaluation. Blinding of endoscopists to patients symptoms and central video reading was not feasible given restrictions in terms of equipment and limited space at 4559m. Intake of dexamethasone and NSAIDs are potential confounders. However, when looking at patients without the intake of ulcerogenic medication at the time of endoscopy, similar increase in rates of endoscopic lesions and peptic ulcer disease were seen over time. In addition, dexamethasone was not started before evening of day 2 (=after follow-up endoscopy). To further limit the counfounding impact of ulcerogenic medications, we only looked at patients with development of peptic lesions at day 2 for our mRNA analyses (before dexamethasone intake). Our study relied on mRNA levels only and did not include analyses of protein expression. Therefore, we cannot exclude that *HIF1A* protein expression was affected by protein degradation as previously described.[28] Finally we cannot exclude that heavy exercise might have affected gastrointestinal perfusion and thereby our endoscopic findings. However, this is less likely the case particularly for the second follow-up endoscopy.

In conclusion, fast ascent to high altitude results in rapid onset of mucosal lesions (including ulcer disease) in a high proportion of otherwise healthy subjects. These lesions were associated with reduced sensation of hunger and are, therefore, clinically meaningful in the presentation of AMS. *HIF2A*-induced *ICAM1* upregulation might be a pathogenic factor for hypoxia-induced peptic lesions and this mechanism may also underlie the occurrence of flares that occur in IBD patients at high altitude. This axis warrants further mechanistic studies.

LEGENDS

Table 1: Patient demographics and baseline characteristics at 490m

Table 2: Comparison between patients with vs. without endoscopic lesions at day 4

Figure 1: Percentage of patients with endoscopic lesions at baseline and day 2, 4 after rapid ascent to 4559m. Frequency of mucosal lesions increases from 12% (baseline) to 26.3% (d2) and 60.9% (d4). The incidence of peptic ulcer disease rises from 0.0% to 10.5% (d2) and 21.7% (d4). Dark gray indicates ulcers, while light gray indicates mucosal lesions.

Figure 2: Representative endoscopic pictures showing development of erosions and ulcerations in the duodenum at 4559m. Arrows point on erosion (picture on the left) and ulceration (two pictures on the right).

Figure 3: Heatmap for mRNA expression levels (compared to baseline) in patients with vs. without endoscopic lesions. Numbers indicate fold change. Green color indicates upregulation, red color means downregulation.

Figure 4: *HIF2A* and *ICAM1* mRNA expression levels (compared to baseline) in patients with vs. without endoscopic lesions. *p=0.011, **p=0.001

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